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(57) Abstract

This invention is a pharmaceutical composition that inhibits the growth of cancers and tumors in mammals, particularly in human and warm blooded animals. The composition is also effective against viruses. The composition contains N-phosphonoglycine derivatives which are systemic herbicides. The composition can also contain N-phosphonoglycine derivatives in combination with chemotherapeutic agents for treatment of cancers and tumors. Optionally potentiators can be included. N-phosphonoglycine derivatives with a potentiator can be used to treat viral infections.

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A PHARMACEUTICAL COMPOSITION CONTAINING N-PHOSPHONOGLYCINE DERIVATIVES FOR INHIBITING THE GROWTH OF VIRUSES AND CANCERS

TECHNICAL FIELD

This invention is a pharmaceutical composition that inhibits the growth of cancers and tumors in mammals, particularly in human and warm blooded animals. The composition is also effective against viruses. The composition contains N-phosphonoglycine derivatives which are systemic herbicides.

BACKGROUND OF THE INVENTION

Cancers are the leading cause of death in animals and humans. The exact cause of cancer is not known, but links between certain activities such as smoking or exposure to carcinogens and the incidence of certain types of cancers and tumors has been shown by a number of researchers.

Many types of chemotherapeutic agents have been shown to be effective against cancers and tumor cells, but not all types of cancers and tumors respond to these agents. Unfortunately, many of these agents also destroy normal cells. The exact mechanism for the action of these chemotherapeutic agents are not always known.

Despite advances in the field of cancer treatment the leading therapies to date are surgery, radiation and chemotherapy. Chemotherapeutic approaches are said to fight cancers that are metastasized or ones that are particularly aggressive. Such cytocidal or cytostatic agents work best on cancers with large growth factors, i.e., ones whose cells are rapidly dividing. To date, hormones, in particular estrogen, progesterone and testosterone, and some antibiotics produced by a variety of microbes, alkylating agents, and anti-metabolites form the bulk of therapies available to oncologists. Ideally cytotoxic agents that have specificity for cancer and tumor cells while not affecting normal cells would be extremely desirable. Unfortunately, none have been found and instead agents which target especially rapidly dividing cells (both tumor and normal) have been used.

Clearly, the development of materials that would target tumor cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to tumor cells while exerting mild effects on normal cells would be desirable. Therefore, it is an object of this invention to provide a pharmaceutical composition that is effective in inhibiting the growth of tumors and cancers in mammals with mild or no effects on normal cells.

More specifically, it is an object of this invention to provide an anti-cancer composition comprising a pharmaceutical carrier and an N-phosphonoglycine derivative as defined herein along with a method of treating such cancers.

It is believed that the phosphonoglycine derivatives in combination with chemotherapeutic agents can suppress and reduce the growth of cancer cells, including leukemia. Therefore, it is an object of this invention to provide a pharmaceutical composition that is effective in both suppressing and inhibiting the growth of tumors and cancers in mammals.

It has been found that the N-phosphonoglycines are especially effective in suppressing the growth of the cancer, tumor, virus, or bacteria. The use of these N-phosphonoglycines in combination with other chemotherapeutic agents which are effective in destroying the tumor is a novel method of treatment.

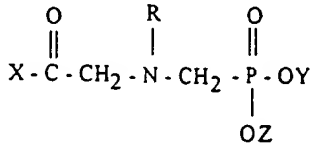
More specifically, it is an object of this invention to provide an anti-cancer composition comprising a pharmaceutical carrier and an N-phosphonoglycine derivative and a chemotherapeutic agent as defined herein along with a method of treating such cancers.

These phosphonoglycines compositions along with potentiators are also effective against viruses. The phosphonoglycine compositions can be used to treat viral infections. Therefore, it is a further object of this invention to provide a method of treating viral infections such as HIV, influenza and rhinoviruses.

These and other objects will become evident from the following detailed description of this inventions.

SUMMARY OF THE INVENTION

A pharmaceutical composition for treatment of mammals, and in particular, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount anti-cancer compound selected from the group consisting of N-phosphonoglycine derivatives of the formula:



wherein X is selected from the group consisting of hydroxy, alkoxy or chloroxy up to 12 carbon atoms; lower alkenoxy, cyclohexyloxy, morpholino, pyrrlidinyl, piperidino and NHR'; Y and Z each independently selected from hydrogen and lower alkyl; and R is selected from the group consisting of hydrogen, formyl, acetyl, benzoyl, nitrobenzoyl and chlorinated benzoyl; and R' is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms, phenyl, chlorinated phenyl and anisyl; and certain salts of these compounds, which salts are selected from the group consisting of the Group I and II metals having an atomic number of up to 30, hydrochloride, acetate, solicylate, pyridine, ammonium, lower aliphatic hydrocarbon amine, lower alkanol amine and aniline.

A pharmaceutical composition for treatment of mammals, and in particular, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount of a

chemotherapeutic agent and an anti-cancer compound selected from the group consisting of N-phosphonoglycine derivatives as defined above. Potentiators can also be used in these compositions.

These compositions can be used to inhibit the growth of cancers and other tumors in humans or animals by administration of an effective amount of the N-phosphonoglycine derivatives either orally, rectally, topically or parenterally, intravenously, or by direct injection near or into the tumor. These compositions are effective in killing or slowing the growth of tumors, yet are safer than adriamycin on normal, healthy cells.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions:

As used herein, the term "comprising" means various components can be conjointly employed in the pharmaceutical compositon of this invention. Accordingly, the terms "consisting essentially of" and "consisting of" are embodied in the term comprising.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

As used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the type of mammal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives.

As used herein, a "pharmaceutical addition salts" includes a pharmaceutically acceptable salt of the anti-cancer compound with an organic or inorganic acid and the amine salts of the acid.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the anti-cancer agent to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

As used herein, "cancer" refers to all types of cancers or neoplasm or tumors found in mammals, including leukemia.

As used herein, the "anti-cancer compounds" are the N-phosphonoglycines, and their salts. The exact N-phosphonoglycines are described in detail below. The preferred material is the products sold under the name glyphosate® or Roundup® by Monsanto. It is N-(phosphonomethyl) glycine.

As used herein, "viruses" includes viruses which cause diseases in warm blooded animals including HIV, influenza, rhinoviruses, herpes and the like.

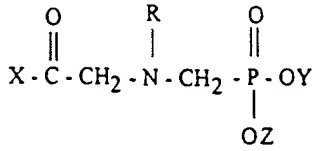
As used herein "chemotherapeutic agents" includes DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others, such as Asparaginase or hydroxyurea.

As used herein "potentiators" are materials such as triprolidine and its cis-isomer or procodazole which are used in combination with the chemotherapeutic agents and the phosphonoglycines.

B. THE ANTI-CANCER COMPOUNDS

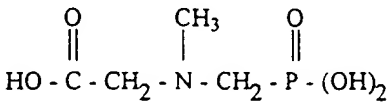
The anti-cancer compounds are N-phosphonoglycine derivatives which are known for their herbicidal activities. They are systemic herbicides used to prevent and eradicate certain plants or weeds. Systemic herbicides are differentiated from other herbicides by their ability to move through the plant. It is not a requirement of this invention that the anti-cancer compounds have this ability.

The compounds have the following structure



wherein X is selected from the group consisting of hydroxy, thioyl, alkoxy or chloroxy up to 12 carbon atoms; lower alkenoxy, cyclohexyloxy, morpholino, pyrrlidinyl, piperidino and NHR'; Y and Z each independently selected from hydrogen and lower alkyl; and R is selected from the group consisting of hydrogen, formyl, acetyl, benzoyl, nitrobenzoyl and chlorinated benzoyl; and R' is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms, phenyl, chlorinated phenyl and anisyl; and certain salts of these compounds, which salts are selected from the group consisting of the Group I and II metals having an atomic number of up to 30, hydrochloride, pyridine, ammonium, lower aliphatic hydrocarbon amine, lower alkanol amine and aniline.

The most preferred compounds are those with the following structure:



The lower alkylamine salts, in particular the isopropyl amine salts, are preferred.

These compounds are prepared according to the method described in U.S. 3,794,758 issued to Franz, Dec. 10, 1974.

C. CHEMOTHERAPEUTIC AGENTS

The chemotherapeutic agents are generally grouped as DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others such as Asparaginase or hydroxyurea. Each of the groups of chemotherapeutic agents can be further divided by type of activity or compound. The chemotherapeutic agents used in combination with the phosphonoglycines of this invention include members of all of these groups. For a detailed discussion of the chemotherapeutic agents and their method of administration, see Dorr, et al, *Cancer Chemotherapy Handbook*, 2d edition, pages 15-34, Appleton & Lange (Connecticut, 1994) herein incorporated by reference.

DNA-Interactive Agents include the alkylating agents, e.g. Cisplatin, Cyclophosphamide, Altretamine; the DNA strand-breakage agents, such as Bleomycin; the intercalating topoisomerase II inhibitors, e.g., Dactinomycin and Doxorubicin); the nonintercalating topoisomerase II inhibitors such as, Etoposide and Teniposde; and the DNA minor groove binder Plcamydin.

The alkylating agents form covalent chemical adducts with cellular DNA, RNA, and protein molecules and with smaller amino acids, glutathione and similar chemicals. Generally, these alkylating agents react with a nucleophilic atom in a cellular constituent, such as an amino, carboxyl, phosphate, sulfhydryl group in nucleic acids, proteins, amino acids, or glutathione. The mechanism and the role of these alkylating agents in cancer therapy is not well understood. Typical alkylating agents include:

Nitrogen mustards, such as Chlorambucil, Cyclophosphamide, Isofamide, Mechlorethamine, Melphalan, Uracil mustard;

Aziridine such as Thiotepa

methanesulphonate esters such as Busulfan;

nitroso ureas, such as Carmustine, Lomustine, Streptozocin;

platinum complexes, such as Cisplatin, Carboplatin;

bioreductive alkylator, such as Mitomycin, and Procarbazine, Dacarbazine and Altretamine;

DNA strand breaking agents include Bleomycin;

DNA topoisomerase II inhibitors include the following:

Intercalators, such as Amsacrine, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, and Mitoxantrone;

nonintercalators, such as Etoposide and Teniposide.

The DNA minor groove binder is Plicamycin.

The antimetabolites interfere with the production of nucleic acids by one or the other of two major mechanisms. Some of the drugs inhibit production of the deoxyribonucleoside triphosphates that are the immediate precursors for DNA synthesis, thus inhibiting DNA replication. Some of the compounds are sufficiently like purines or pyrimidines to be able to substitute for them in the anabolic nucleotide pathways. These analogs can then be substituted into the DNA and RNA instead of their normal counterparts. The antimetabolites useful herein include:

folate antagonists such as Methotrexate and trimetrexate

pyrimidine antagonists, such as Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine, Cytarabine, and Floxuridine

purine antagonists include Mercaptopurine, 6-Thioguanine, Fludarabine, Pentostatin;

sugar modified analogs include Cyctrabine, Fludarabine;

ribonucleotide reductase inhibitors include hydroxyurea.

Tubulin Interactive agents act by binding to specific sites on tubulin, a protein that polymerizes to form cellular microtubules. Microtubules are critical cell structure units. When the interactive agents bind on the protein, the cell can not form microtubules Tubulin Interactive agents include Vincristine and Vinblastine, both alkaloids and Paclitaxel.

Hormonal agents are also useful in the treatment of cancers and tumors. They are used in hormonally susceptible tumors and are usually derived from natural sources. These include:

estrogens, conjugated estrogens and Ethinyl Estradiol and Diethylstilbesterol, Chlortrianisen and Idenestrol;

progestins such as Hydroxyprogesterone caproate, Medroxyprogesterone, and Megestrol;

androgens such as testosterone, testosterone propionate; fluoxymesterone, methyltestosterone;

Adrenal corticosteroids are derived from natural adrenal cortisol or hydrocortisone. They are used because of their anti inflammatory benefits as well as the ability of some to inhibit mitotic divisions and to halt DNA synthesis. These compounds include, Prednisone, Dexamethasone, Methylprednisolone, and Prednisolone.

Leutinizing hormone releasing hormone agents or gonadotropin-releasing hormone antagonists are used primarily the treatment of prostate cancer. These include leuprolide acetate and goserelin acetate. They prevent the biosynthesis of steroids in the testes.

Antihormonal antigens include:

antiestrogenic agents such as Tamosifen,

antiandrogen agents such as Flutamide ; and

antiadrenal agents such as Mitotane and Aminoglutethimide.

Hydroxyurea appears to act primarily through inhibition of the enzyme ribonucleotide reductase.

Asparagenase is an enzyme which converts asparagine to nonfunctional aspartic acid and thus blocks protein synthesis in the tumor.

D. POTENTIATORS

The "potentiators" can be any material which improves or increase the efficacy of the pharmaceutical composition or is an immunosuppressor. One such potentiator is triprolidine and its cis-isomer which are used in combination with the chemotherapeutic agents and the N-phosphonoglycine derivative. Triprolidine is described in US 5,114,951 (1992).

Another potentiator is procodazole, 1H-Benzimidazole-2-propanoic acid; [ß-(2-benzimidazole] propionic acid; 2-(2-carboxyethyl)benzimidazole; propazol]. Procodazole is a non-specific active immunoprotective agent against viral and bacterial infections and can be used with the compositions claimed herein. It is effective with the N-phosphonoglycines alone in treating cancers, tumors, leukemia and viral infections or when combined with N-phosphonoglycine derivatives and chemotherapeutic agents.

Propionic acid and its salts and esters can also be used in combination with the pharmaceutical compositions claimed herein.

Antioxidant vitamins such as vitamins A, C and E and beta-carotene can be added to these compositions.

E. DOSAGE

Any suitable dosage may be given in the method of the invention. The type of compound and the carrier and the amount will vary widely depending on the species of the warm blooded animal or human, body weight, and tumor being treated. For the chemotherapeutic agents a lower dosage of from 0.5 mg/kg body weight to about 400 mg/kg body weight is acceptable. Generally a dosage of between about 2 milligrams (mg) per kilogram (kg) of body weight and about 400 mg per kg of body weight is suitable. Preferably from 15 mg to about 150 mg/kg of body weight is used. Generally, the dosage in man is lower than for small warm blooded mammals such as mice. A dosage unit may comprise a single compound or mixtures thereof with other compounds or other cancer inhibiting compounds. The exact range and ratio of the chemotherapeutic agent to the N-phosphonoglycine will depend on the type of chemotherapeutic agent and the cancer being treated. The dosage unit can also comprise diluents, extenders, carriers and the like. The unit may be in solid or gel form such as pills, tablets, capsules and the like or in liquid form suitable for oral, rectal, topical or parenteral administration or intravenous administration or injection into or around the tumor site.

F. DOSAGE DELIVERY FORMS

The anti-cancer compounds and optionally the chemotherapeutic agent and/or the potentiator, are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid or liposome and the type is generally chosen based on the type of administration being used. The active agent can be coadministered in the form of a tablet or capsule, as an agglomerated powder or in a liquid form. Examples of solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups, elixirs, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted

from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners and melting agents. Oral dosage forms would contain flavorants and coloring agents. Parenteral and intravenous forms would also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in US. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

G. METHOD OF TREATMENT

The method of treatment can be any suitable method which is effective in the treatment of the particular virus, cancer or tumor type that is being treated. Treatment may be oral, rectal, topical, parenteral, intravenous or injection into or around the tumor site and the like. The method of applying an effective amount also varies depending on the tumor being treated. It is believed that parenteral treatment by intravenous, subcutaneous, or intramuscular application, formulated with an appropriate carrier, additional cancer inhibiting compound or compounds or diluent to facilitate application will be the preferred method of administering the compounds to warm blooded animals.

It is believed that many herbicides alone or in combination with other herbicides and/or fungicides will show this beneficial anti-tumor effect. Preferred fungicides include the benzimidazole fungicides such as carbendazim, thiabendazole, benomyl. Other agents which can be used include griseofulvin, fluconazole and propiconazole.

The N-phosphonoglycine derivatives are also effective against viruses including rhinovirus, HIV, herpes, and influenza. The combination of the N-phosphonoglycines with potentiators are especially effective against viruses. The dosage form and method of treatment is the same as for tumors or cancer.

The following examples are illustrative and are not meant to be limiting to the invention.

Colon, Breast and Lung Tumor Cells Test

The following cell culture tests were performed to test the toxicity of the N-phosphonoglycine compounds on colon, breast and lung human tumor cells. The viability of the cells were tested by looking at MTT (3-[4,5-dimethylthiazol-2-yl] -2,5-diphenyltetrazolium bromide) reduction. MTT assay is a well known measure of cell viability.

The colon tumor cells (HT29 from American Type Culture Collection (ATCC)) and the breast cells (MX1 from cell lines from ATCC) were cultured in Eagle's Minimal Essential Medium

with 10% fetal bovine serum. The lung tumor cells (A549 from ATCC cell lines) were cultured in Ham's F12 medium with 10% fetal bovine serum.

The tumor cells were passaged and seeded into culture flasks at the desired cell densities. The culture medium was decanted and the cell sheets were washed twice with phosphate buffered saline (PBS). The cells were trypsinized and triturated prior to seeding the flasks. Unless otherwise indicated the cultures were incubated at 37 ± 1° C in a humidified atmosphere of 5± 1% carbon dioxide in air. The cultures were incubated until they were 50-80% confluent.

The cells were subcultured when the flasks were subconfluent. The medium was aspirated from the flasks and the cell sheets rinsed twice with PBS. Next, the Trypsin Solution was added to each flask to cover the cell sheet. The Trypsin Solution was removed after 30-60 seconds and the flasks were incubated at room temperature for two to six minutes. When 90% of the cells became dislodged, growth medium was added. The cells were removed by trituration and transferred to a sterile centrifuge tube. The concentration of cells in the suspension was determined, and an appropriate dilution was made to obtain a density of 5000 cells/ml. The cells were subcultured into the designated wells of the 96-well bioassay plates (200 microliter cell suspension per well). PBS was added to all the remaining wells to maintain humidity. The plates were then incubated overnight before test article treatment.

Each dose of test article was tested by treating quadruplicate wells of cultures with 100 microliter of each dilution. Those wells designated as solvent controls received an additional 100 microliter of methanol control; negative controls wells received an additional 100 microliters of treatment medium. PBS was added to the remaining wells not treated with test article or medium. The plates were then incubated for approximately 5 days.

At the end of the 5 day incubation, each dose group was examined microscopically to assess toxicity. A 0.5 mg/ml dilution of MTT was made in treatment medium, and the dilution was filtered through a 0,.45 micrometer filter to remove undissolved crystals. The medium was decanted from the wells of the bioassy plates. Immediately thereafter, 2000 microliter of the filtered MTT solution was added to all test wells except for the two untreated blank test wells. The two blank wells received 200 microliters of treatment medium. The plates were returned to the incubator for about 3 hours. After incubation, the MTT containing medium was decanted. Excess medium was added to each well and the plates were shaken at room temperature for about 2 hours.

The absorbance at 550 nm (OD_{550}) of each well was measured with a Molecular Devices (Menlo Park, CA) VMax plate reader.

The mean OD_{550} of the solvent control wells and that of each test article dilution, and that of each of the blank wells and the positive control were calculated. The mean OD_{550} of the blank wells was subtracted from the mean of the solvent control wells, and test article wells, respectively to give the corresponding mean OD_{550}.

$$\% \text{ of Control} = \frac{\text{corrected mean OD550 of Test Article Dilution}}{\text{corrected mean of OD550 of Solvent Control}} \times 100$$

Dose response curves were prepared as semi-log plots with % of control on the ordinate (linear) and the test article concentration on the abscissa (logarithmic). The EC_{50} was interpolated from the plots for each test article.

For the test articles administered in methanol, separate responses were prepared to correct for the methanol data.

Adriamycin was used as a positive control. In all cases, it was more toxic than any of the test materials by one or two logs. Adriamycin is one of the more potent agents in current use and one with significant side effects. The peak plasma concentration of other, quite effective chemotherapeutic agents may be 10 to 50 times higher than that of Adriamycin. The EC-50 is the concentration at which one half the cells are killed.

Table 1

Test Material	EC-50 Result (ppml)					
	HT29	HT29	MX1	MX1	A549	A549
Adriamycin	0.003	0.006	0.02	0.001	0.03	0.009
glyophsate	5.41	3.73	36.5	14.6	25.9	22.3

In normal healthy cells, the following results were obtained:

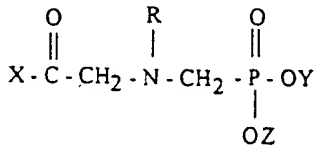
Table 2

Test Material	EC-50					
	Broncheal Cells		Kerotinovle Cells		Fibroblasts	
glyphosate	1.59	3.54	3.09	3.21	86.1	35.8
Adriamycin	0.015	0.0020	0.0035	0.0093	0.065	0.10

These experiments show that these compositions are effective in killing tumor cells without significantly affecting healthy cells. They are safer than adriamycin.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating cancers, tumors or viral infections comprising a safe and effective amount of N-phosphonoglycine derivatives of the formula:



wherein X is selected from the group consisting of hydroxyl, alkoxy or chloroxyl up to 12 carbon atoms; lower alkenoxy, cyclohexyloxy, morpholino, pyrrlidinyl, piperidino and NHR'; Y and Z each independently selected from hydrogen and lower alkyl; and R is selected from the group consisting of hydrogen, formyl, acetyl, benzoyl, nitrobenzoyl and chlorinated benzoyl; and R' is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms, phenyl, chlorinated phenyl and anisyl; and certain salts of these compounds, which salts are selected from the group consisting of the Group I and II metals having an atomic number of up to 30, hydrochloride, acetate, salicylate, pyridine, ammonium, lower aliphatic hydrocarbon amine, lower alkanol amine and aniline.

2. A pharmaceutical composition according to Claim 1 which additionally comprises a potentiator.

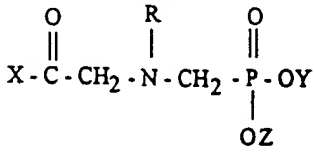
3. A pharmaceutical composition according to Claim 1 or 2 which additionally comprises a chemotherapeutic agent.

4. A pharmaceutical composition according to Claim 1,2 or 3 comprising a pharmaceutically acceptable carrier and a safe and effective amount of a N-(phosphonomethyl) glycine and/or its isopropyl amine salt and wherein said pharmaceutical acceptable acid addition salts are selected from the group consisting of hydrochloride, acetate, salicylate, lower alkyl amine and mixtures thereof.

5. A pharmaceutical composition according to Claim 1,2,3 or 4 wherein said chemotherapeutic agent is selected from the group consisting of DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents Asparaginase or hydroxyurea, Asparaginase, hydroxyurea, Cisplatin, Cyclophosphamide, Altretamine, Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposde, and Plcamydin, Methotrexate, Fluorouracil, Fluorodeoxyuridine, CB3717, Azacitidine, Cytarabine, Floxuridine, Mercaptopurine, 6-Thioguanine, Fludarabine, Pentostatin, Cyctrabine, and Fludarabine.

6. A method of treating cancer and viral infections in warm blooded mammals comprising administering a safe and effective amount of a pharmaceutical composition according to claims 1,2,3,4 or 5.

7. A unit dosage composition for treating tumors or viral infections comprising a N-phosphonoglycine derivatives of the formula:



wherein X is selected from the group consisting of hydroxyl, alkoxy or chloroxyl up to 12 carbon atoms; lower alkenoxy, cyclohexyloxy, morpholino, pyrrlidinyl, piperidino and NHR'; Y and Z each independently selected from hydrogen and lower alkyl; and R is selected from the group consisting of hydrogen, formyl, acetyl, benzoyl, nitrobenzoyl and chlorinated benzoyl; and R' is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms, phenyl, chlorinated phenyl and anisyl; and certain salts of these compounds, which salts are selected from the group consisting of the Group I and II metals having an atomic number of up to 30, hydrochloride, pyridine, ammonium, lower aliphatic hydrocarbon amine, lower alkanol amine and aniline.

8. A unit dosage composition according to Claim 7 wherein said N-phosphonoglycine is N-(phosphonomethyl) glycine and its lower alkyl amine salts.

9. A unit dosage composition according to Claim 6, 7 or 8 wherein said pharmaceutical acceptable acid addition salts are selected from the group consisting of and mixtures thereof hydrochlorides, acetates and salicylates and wherein from about 2 mg/kg body weight to about 400 mg/kg of said N-phosphonoglycine is administered.

10. A unit dosage composition according to claim 9 further comprising a safe and effective amount of a chemotherapeutic agent

11. A unit dosage composition according to Claim 10 wherein said N-phosphonoglycine is N-(phosphonomethyl) glycine and its lower alkyl amine salts. and wherein said pharmaceutical acceptable acid addition salts are selected from the group consisting of and mixtures thereof hydrochlorides, acetates and salicylates.

12. A method of inhibiting the growth of tumors comprising administering a safe and effective amount of a systemic herbicide.

13. A unit dosage composition for inhibiting the growth of tumors comprising a safe and effective amount of a systemic herbicide.

14. A unit dosage composition for inhibiting the growth of tumors comprising a safe and effective amount of a systemic herbicide, a fungicide and a chemotherapeutic agent.

15. A unit dosage composition according to Claim 10,11,12,13 or 14 which additionally comprises a potentiator.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/04954

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ARCH.IMMUNOL.THER.EXP., vol. 33, no. 219, 1985, pages 325-329, XP000579382 DUS ET AL.: "Cytostatic activity in vitro of phosphonic acid derivatives" see p. 325, table 1, compound no. 4 see page 328, line 25 - line 30 ---	1-15
A	PHARM.CHEM.J., vol. 12, 1978, pages 1428-1431, XP000579394 BANDURINA ET AL.: "Synthesis and antitumor activity of aminophosphonic acids" see page 1428, paragraph 1 see page 1429, paragraph 1 see page 1430; table 2 ---	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
21 August 1996	05. 09. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Gerli, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/04954

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TROP.AGRIC.RES.SER., vol. 19, 1985, pages 195-208, XP000579507 MOCHIDA ET AL.: "Chemical control of green leafhoppers to prevent virus diseases, especially tungro disease, on susceptible intermediate rice cultivars in the tropics" see page 206; table 7 ---	1-15
A	US,A,5 114 951 (KING) 19 May 1992 cited in the application see claim 1 -----	1-15

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/04954

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 6, 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the description, p.1, l.3-4, claims 12-15 have been read and searched as being limited to the compounds of claim 1 .

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/04954

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5114951	19-05-92	NONE	